Universidade de Aveiro Departamento de Ciências Médicas
Ano 2016

GUILHERME DE SOUSA LUZ

RELATÓRIO DE ESTÁGIO CURRICULAR EM MONITORIZAÇÃO DE ESTUDOS CLÍNICOS NUMA CRO *FULL SERVICE*

CURRICULAR INTERNSHIP REPORT IN CLINICAL STUDIES MONITORING AT A FULL SERVICE CRO

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção de grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica de Maria João Santos, Scientific and Quality Assurance Manager da DATAMEDICA – Serviços e Consultoria em Bioestatística, Lda., e do Professor Doutor Bruno Gago, Professor Auxiliar Convidado do Departamento de Ciências Médicas da Universidade de Aveiro.

Curricular internship report presented to University of Aveiro to fullfil the necessary requeirements to the Master of Science Degree in Pharmaceutical Medicine, held under the scientific guidance of Maria João Santos, Scientific and Quality Assurance Manager at DATAMEDICA – Serviços e Consultoria em Bioestatística, Lda., and Professor Bruno Gago, Ph.D., Invited Assistant Professor at the Medical Sciences Department of the University of Aveiro.

I dedicate this work to my parents, who supported me throughout this entire journey.

“Your vision of where or who you want to be is the greatest asset you have.” (Paul Arden)

o júri

Presidente	Professor Doutor Nelson Fernando Pacheco da Rocha Professor Catedrático da Universidade de Aveiro
Vogal – arguente principal	Professora Doutora Maria Joana da Costa Gomes da Silva Professora Adjunta da Universidade de Aveiro
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agradecimentos

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palavras-chave

Estágio, CRO *Full Service*, Estudos Clínicos, Investigação Clínica, Monitorização, Biomedicina Farmacêutica

resumo

O presente relatório tem como fim descrever as atividades desenvolvidas e experiência e competências adquiridas durante o estágio curricular numa CRO *Full Service*, a DATAMEDICA – Consultoria e Serviços em Bioestatística, Lda., no âmbito do Mestrado em Biomedicina Farmacêutica. O principal objectivo do estágio foi adquirir conhecimento e competências inerentes ao desempenho do trabalho de *Clinical Research Associate.*

O estágio curricular teve a duração de 8 meses, compreendidos entre setembro de 2015 e abril de 2016, tendo o estágio na DATAMEDICA, no entanto, começado em junho de 2015. Este estágio permitiu a realização de várias funções na área da Investigação Clínica, destacando-se a Submissão e Monitorização de Estudos Clínicos, Escrita Médica e Gestão de Dados.

Neste estágio foi possível aplicar conteúdos teóricos obtidos durante o Mestrado em Biomedicina Farmacêutica e desenvolver competências necessárias, principalmente, à monitorização de ensaios clínicos, mas também às outras atividades supramencionadas. Para além disso, a integração numa equipa multidisciplinar no meio empresarial e interação, aquando fora da empresa, com outros profissionais da área médica e da investigação clínica resultou num crescimento pessoal e profissional.

Na secção do estado da arte são abordados temas como a investigação clínica, evolução do ambiente regulamentar a nível global ao longos dos anos. É também feito um panorama dos ensaios clínicos a nível nacional.

keywords

Internship, CRO Full Service, Clinical Studies, Clinical Research, Monitoring, Pharmaceutical Medicine

abstract

The present report aims at describing the developed activities and experiences and skills acquired during the curricular internship at a Full Service CRO, *DATAMEDICA – Consultoria e Serviços em Bioestatística, Lda.*, in the scope of the Pharmaceutical Medicine Master of Science. The main objective of the internship was to acquire knowledge and skills inherent to performing the Clinical Research Associate job.

The curricular internship had a duration of 8 months, from September 2015 until April 2016, having the internship at DATAMEDICA, however, started in June 2015. This internship allowed several roles in the Clinical Investigation area to be performed, highlighting the Clinical Studies' Submission and Monitoring, Medical Writing and Data Management activities.

In this internship it was possible to put into use theoretical concepts obtained during the Pharmaceutical Medicine Master of Science and to develop skills necessary, mainly, to the clinical study monitoring, but also to the other above-mentioned activities. Beyond this, the integration in a multidisciplinary team in a business environment and interaction, when outside the company, with other medical and clinical investigation professionals has resulted in a personal and professional growth.

In the state of the art section, clinical investigation and the evolution of the global regulatory environment are mentioned. A panorama of the clinical trials on a national scale is also made.

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LIST OF ABBREVIATIONS

AB Administration Board

AE Adverse Event

ATC Anatomical Therapeutic Chemical

B.Sc. Bachelors of Science

CA Competent Authority

CEIC *Comissão de Ética para a Investigação Clínica* (National Ethics Committee for Clinical Research)

CNPD *Comissão Nacional de Proteção de Dados* (National Data Protection Commission)

COV Close-Out Visit

CRA Clinical Research Associate

CRF Case Report Form

CRO Contract Research Organisation

CS Candidate Selection

CTA Clinical Trial Application

CTD Common Technical Document

eCRF Electronic Case Report Form

EC European Commission

EEA European Economic Area

EMA European Medicines Agency

EU European Union

EudraCT European Union Drug Regulating Authorities Clinical Trials

FDA United States Food and Drug Administration

FED First Efficacy Dose

FHD First Human Dose

GCP	Good Clinical Practice
HC	Host Company
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Products
INFARMED	*Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* (National Authority of Medicines and Health Products, I.P.)
M.Sc.	Masters of Science
MS	Member State
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
NME	New Molecular Entity
PD	Product Decision
PIS	Patient Information Sheet
POC	Proof-Of-Concept
p(TS)	Probability of Success
R&D	Research and Development
SAE	Severe Adverse Event
SDV	Source Data Verification
SIV	Site Initiation Visit
SMF	Study Master File
SOP	Standard Operating Procedure

1. INTRODUCTION

The present report consists of an overview of the activities performed as a Clinical Research Associate (CRA) trainee in a Portuguese Contract Research Organisation (CRO). Despite holding a CRA trainee position, I had the opportunity to execute several tasks inherent to other roles were executed by me, such as Medical Writing, Data Management and Quality Assurance activities. This in-the-job experience was performed in the scope of the Masters of Science (M.Sc.) in Pharmaceutical Medicine, whose students are allowed to carry out a curricular internship during the second year of the M.Sc. The M.Sc. in Pharmaceutical Medicine of the University of Aveiro is affiliated to the PharmaTrain programme. It is considered, since late 2013, a PharmaTrain Centre of Excellence.

The curricular internship started in September 14th, 2015 and ended in April 29th, 2016. However, the internship at the host company started in June 1st, 2015. The present report will only focus the activities done in the curricular internship official period. Yet, some aspects of integration in the host company's team, which happened early in June, will be reported by me throughout this report.

DATAMEDICA – Consultoria e Serviços em Bioestatística, Lda. has been the chosen Host Company (HC). The reasons this company was preferred by me to perform the curricular internship were mainly the possibility of doing several tasks, allowing to obtain knowledge and experience in more than one activity; the positive feedback given by some colleagues who took their internship at DATAMEDICA; and the fact it was (and still is) a fully Portuguese capital company.

This report will address the proposed internship objectives; the host company, namely its structure and organisation; the current state of the art in Clinical Research; the difficulty of Portuguese CROs in entering the market of multinational clinical trials; and the most relevant activities performed throughout the internship and how they were performed. In the end, the challenges faced and the main aspects of this in-the-job experience will be discussed, detailing if the proposed objectives were met. The impact the eight-month experience had on my growth as a person and as a professional in the clinical studies field will be the main focus of the conclusion.

1.1. INTERNSHIP OBJECTIVES

The acquisition of knowledge and competences in the clinical studies field, since their conception till their implementation and subsequent results' critical analysis and, at the same time, the consolidation of the acquired knowledge throughout the Bachelors of Science in Biomedical Sciences and M.Sc. in Pharmaceutical Medicine were the main goals of the curricular internship. To achieve the main goals, the accomplishment and development of specific objectives were proposed. The objectives were to:

- Know and apply the main methods used in the conception and development of clinical studies;
- Submit clinical studies application to the *Comissão de Ética para a Investigação Clínica* (CEIC), *Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* (INFARMED), *Comissão Nacional de Proteção de Dados* (CNPD), Hospital Ethic Committees and Hospital Administration Boards;
- Acquire the theoretical and practical knowledge inherent to clinical studies monitoring and develop the necessary skills to perform the CRA job:
    - Accompany the start-up, monitoring and Close Out trial Visits (COVs) in study centres and prepare the respective reports;
    - Assure the clinical studies team follows the specific protocol, ensuring the participant safety and reaching high quality levels regarding the obtained data;
    - Guarantee the clinical study's team is motivated for and during the study.
- Develop the skills and competences inherent to team work and creation of interpersonal relations with the HC colleagues and other professionals of the pharmaceutical industry and health services;
- Support the HC in other clinical research projects being developed which are not directly related with clinical studies monitoring;
- Develop all the work according to the International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs) and Standard Operating Procedures (SOPs) of the HC;
- Maintain a constant and continuous learning process.

1.2. HOST COMPANY

DATAMEDICA is a Portuguese capital full service CRO. A CRO is "a person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions" (1). In other words, a CRO provides scientific expertise and support for pharmaceutical, medical device and biotechnology industries. While hiring a CRO's services, independent companies obtain a broader and time saving experience. This helps in reducing the costs of conducting a clinical trial, for example. A CRO is also requested when a company does not want to hire staff to perform specific tasks.

A full service CRO is one CRO which offers a wide variety of services to the industry while offering and maintaining a single point of contact, largely minimizing the disruption and costs of the sponsor. Hiring a full service CRO is also synonym of having the work done under the scope of the same SOPs. This means all the work done will have the same consistency.

As a Portuguese capital full service CRO, DATAMEDICA has an important role in the clinical research in Portugal. Not having the highest fees in the CROs market, DATAMEDICA is able to provide its services to a wide range of clients. Those clients vary among health care professionals, pharmaceutical industry companies and Portuguese health societies. Despite clinical studies being the major focus of the company, DATAMEDICA is also growing in the medical writing market (2). More and more health care professionals are seeking professional help to improve and publish scientific papers in Portugal nowadays. Having a good service quality and a multidisciplinary team has made DATAMEDICA a company with good reputation among national clinical research stakeholders.

In 1996, when it was created, DATAMEDICA only provided biostatistical consultancy services (2). It was not later on when, due to market needs, those consultancy services were extended to a broader number of services. Nowadays, DATAMEDICA offers support in Clinical and Epidemiological Investigation, Pharmacovigilance, Pharmacoeconomic studies, Medical Writing and Statistical Analysis (2). Supporting Clinical and Epidemiological Investigation means, among other things, providing services in: protocol development and Case Report Form (CRF) design, which together are considered the Study Conception; study submission to the Competent Authorities (CAs); study implementation; study monitoring; and back-office support to both investigational team and study sponsor (2).

Throughout all these years, DATAMEDICA has developed the majority of its clinical trial monitoring in the Respiratory, Endocrinology and Neurology areas (2). Although the more requested areas of its 20-year existence were the aforementioned ones, in the last years there have been accepted more studies in the Rare Diseases and Cardiology areas.

DATAMEDICA, as shown in Figure 1, is composed by an Administration Board (AB), a Financial and Administrative Department, an Executive Management Department and a Scientific Department. It is composed by 9 full-time employees, being some departments only composed by one person. Hence, DATAMEDICA is considered a micro enterprise.

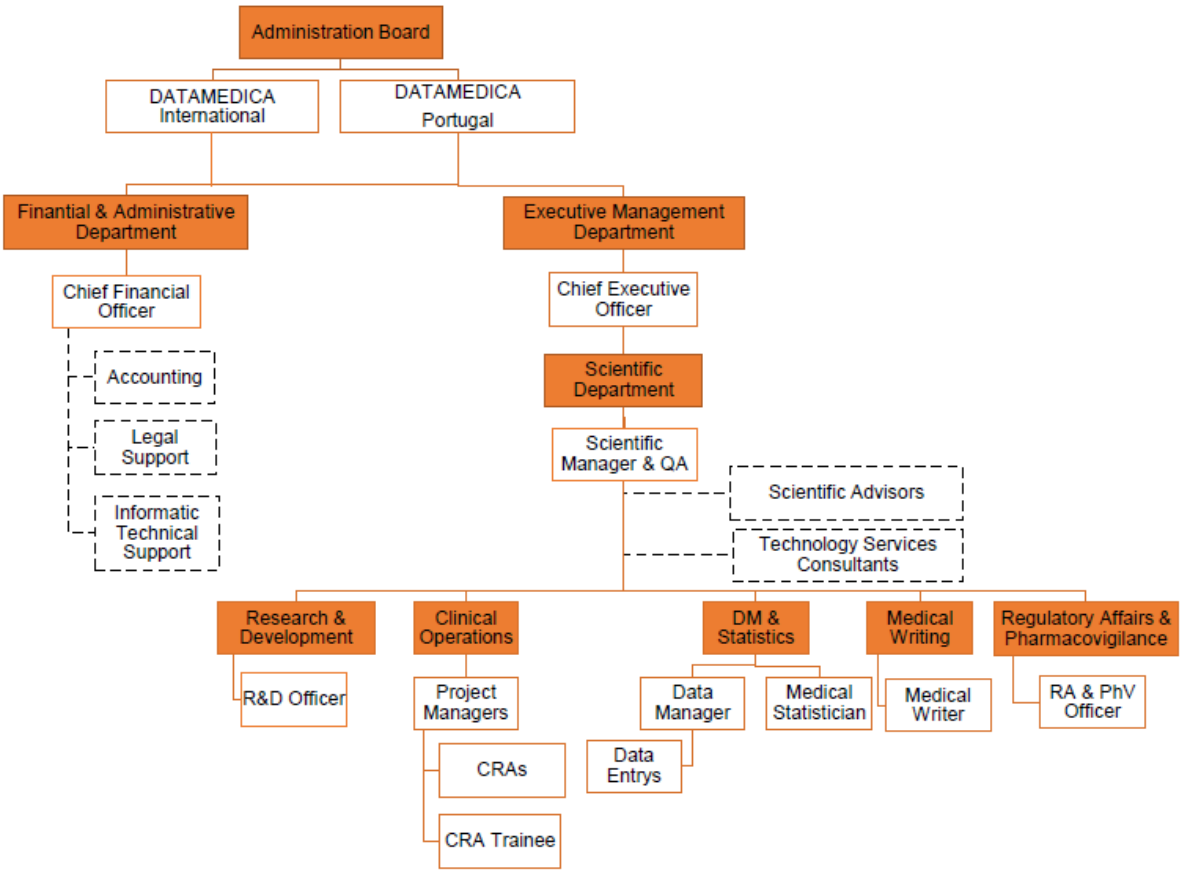

Figure 1. DATAMEDICA's organisational chart (obtained from DATAMEDICA's Internal Documents)

The vast majority of DATAMEDICA's technical and scientific work goes through the Scientific Department. This department is the most branched one. Being divided in several units allows the work to be divided in more specific tasks according to the service being provided. The Research and Development (R&D) unit is responsible for the studies conception and development, bibliographic research inherent to the preparation of the study and development of documents such as the protocol, CRF and Informed Consent Form (ICF). Clinical

studies' submission and monitoring are tasks performed by the Clinical Operations Unit. The Data Management & Statistics Unit is in charge of the data management e.g., database design and query resolution, and the statistics of the study e.g., sample size calculation, analysis planning, clinical interpretation of the data and development of the statistical reports. The development and submission of abstracts, articles and posters are responsibility of the Medical Writing Unit. The Regulatory Affairs & Pharmacovigilance Unit performs pharmacovigilance activities.

1.3. STATE OF THE ART – CLINICAL RESEARCH

1.3.1. Clinical Research

The definition of clinical research is divided in three different parts:

"1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes: (a) mechanisms of human disease, (b), therapeutic interventions, (c) clinical trials, or (d) development of new technologies;

2) Epidemiological and behavioural studies;

3) Outcomes research and health services research" (3).

In a simplistic version, clinical research can be defined as the interventions made in human beings, whose results will be the basis for the approval of new health technologies, supporting the decision to diagnose, treat or for providing a prognosis of the pathologies which affect the patients (4).

Clinical studies have now become a part of physicians' routine medical care (4). Their purpose is to add and enhance the medical field knowledge related to the treatment, diagnosis, and prevention of diseases or conditions (5). Clinical studies are usually done for evaluating one or more interventions for treating a disease, syndrome or condition; finding ways to prevent the initial development or recurrence of a disease or condition; and exploring and measuring ways to improve the comfort and quality of life through supportive care for people with a chronic illness, among others (5). In a broad perspective, clinical studies serve the interests of medicine by exploring the differences and benefits of new and existing medicines, medical devices and vaccines and lifestyle changes as a therapy for different medical conditions (5).

There are two types of clinical studies: interventional studies and non-interventional studies (6). An interventional study is when a participant is submitted to an intervention that changes or influences his health care with the objective of finding or verifying its health effects (5,6). Those interventions may be medical products (e.g., medicines, medical devices or cosmetics), medical procedures and changes in the behaviour (e.g., diet or educational

changes), among others (5,6). Some interventional studies are considered clinical trials, which are explained below (6). In an non-interventional study, investigators assess health outcomes from participants who are submitted to treatments or procedures prescribed according to medical practice (5,6). Those treatments must be used according to the conditions referred in the Marketing Authorisation (MA) (6). The decision to prescribe a treatment to a patient must also be clearly dissociated from the decision of including or not the participant in the study (6).

According to the Portuguese Clinical Investigation Law, a clinical trial is "any investigation conducted in the human being, intended to discover or to verify the clinical, pharmacological our other pharmacodynamical effects of one or more experimental medicines, or to identify the undesirable effects of one or more experimental medicines, or to analyse the absorption, distribution, metabolism and elimination of one or more experimental medicines, in order to ascertain the respective safety or efficacy" (6).

Typically, medicines' clinical trials can be divided in 4 major clinical research phases: Phase I, Phase II, Phase III and Phase IV (7,8). A Phase I trial aims to test the safety and dosage of a medicine (8). This phase is conducted in a small number of healthy volunteers, usually between 20 and 80 (8). A Phase II trial is performed to test the new medicine on a group of patients with the disease/condition which is being studied (7,8). Conducted in several hundred people, this phase aims to study the efficacy and side effects of the medicine, as well as to find the most effective dose (7,8). Then, Phase III trials are implemented. These trials involve several thousands of patients and are used to demonstrate if the product offers a treatment benefit to a specific population (7,8). In sum, their purposes is to study efficacy and to monitor adverse reactions, as most of the safety data is only obtainable in trials who last as long as a Phase III trial (approximate length of 1 to 4 years) (8). A Phase IV trial only takes place when the medicine has been approved by the CAs (7). Efficacy, effectiveness, safety and other patient-related endpoints (e.g. quality of life) are studied in this type of trial (7,8). Phase IV trials are also used to assess the effects of other kind of treatments while combined with the medicine, as it is being performed in "real world" conditions (9). These phases are distinctively showed in Figure 2.

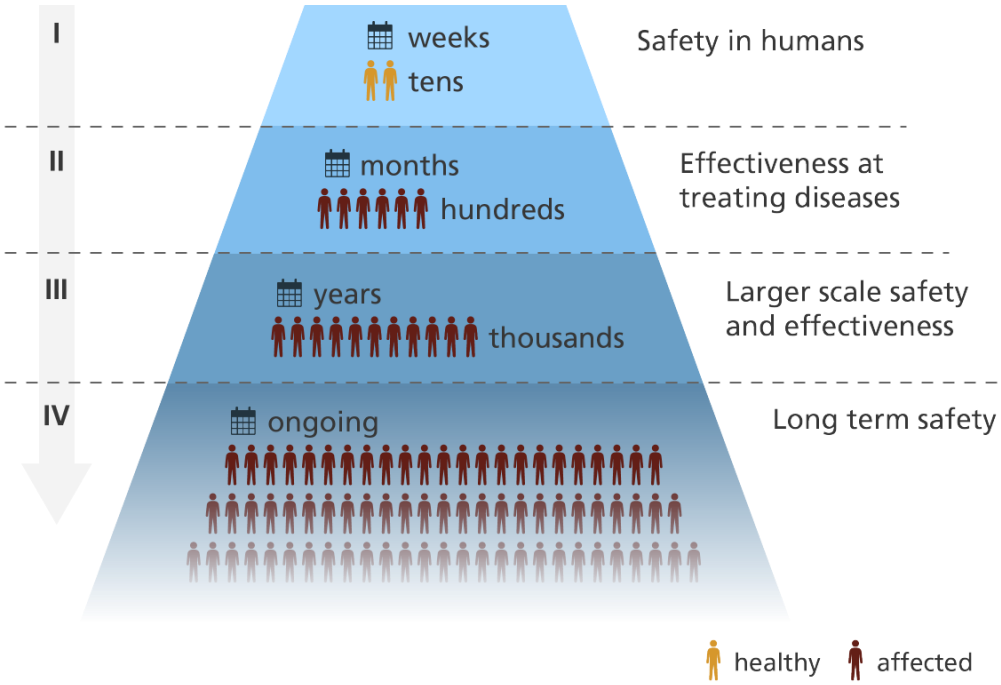

Figure 2. Flow diagram of the different phases in a clinical trial (adapted from (10))

Prone to unsustainable costs, in 2010 a new drug development paradigm emerged (11). This new paradigm, dubbed "quick win, fast fail", is the alternative to the aforementioned one, based on Phase I to Phase III clinical trials before approval (11). The model is meant to demonstrate how R&D productivity, the pharmaceutical industry's grand challenge, can be overcome (11). The need for the productivity increase is correlated with the loss of revenue due to patent expirations for successful products (11). The new paradigm is also connected with the attrition rates of Phase II and Phase III: 66% and 30%, respectively (11). After almost 15 years, those rates have not improved substantially, leading to more and more compounds failing during Phase II and Phase III development (11). Those failures result in major loss of capital by the large pharmaceutical companies (11). In its turn, the loss of capital may impact the health and well-being of patients due to the delayed or even lost opportunities to introduce, test and market the next generation of innovative medicines (11). The launch of new chemical entities was estimated to be responsible for 40% of the 1986-2000 increase in longevity (11).

The “quick win, fast fail” model has been greatly influenced by:

- The uncertainty level in the markets and consequent financing difficulties (4,11);
- The emerging of new markets with great growth potential in medicines’ consumption (4);
- Reduced growth opportunities by fusion and acquisition, due to the high level of the current market consolidation (4). For example, in May 2014, Pfizer tried to buy AstraZeneca for $118 billion, being unsuccessful on this attempt (12). Despite not having success on acquiring a direct competitor, Pfizer in November tried and succeeded in buying the renown Botox maker Allergan Plc for $160 billion (13);
- Growing exposure to generic medicines, considered one of the great competitors of large pharmaceuticals after patent expirations (4,11). Viagra, for example, 4 months after its patent loss in Portugal already had 58 generic brands (14). Generics are also currently approaching 70% of all prescriptions in the United States, resulting in loss of revenue for the former patent owners (11);
- The aging and lifestyle change of the developed countries’ population (4);
- Pressure to reduce costs in the public health systems, as budgets are being constantly strained (4,11).

In sum, Figure 3 illustrates the traditional paradigm of drug development [a] contrasted with an alternative development paradigm [b] (15). In the [b] alternative, “technical uncertainty is intentionally decreased before the expensive later development stages (Phase II and Phase III) through the establishment of Proof-Of-Concept (POC)” (15). “This results in a reduced number of New Molecular Entities (NMEs) advancing into Phase II and III, but those that do advance have a higher probability of success (p(TS)) and launch” (15). “The savings gained from costly investment in late-stage R&D failures are re-invested in R&D to further enhance R&D productivity” (15). In Figure 3, CS stands for candidate selection; FED to first efficacy dose; FHD to first human dose; and PD to product decision (15).

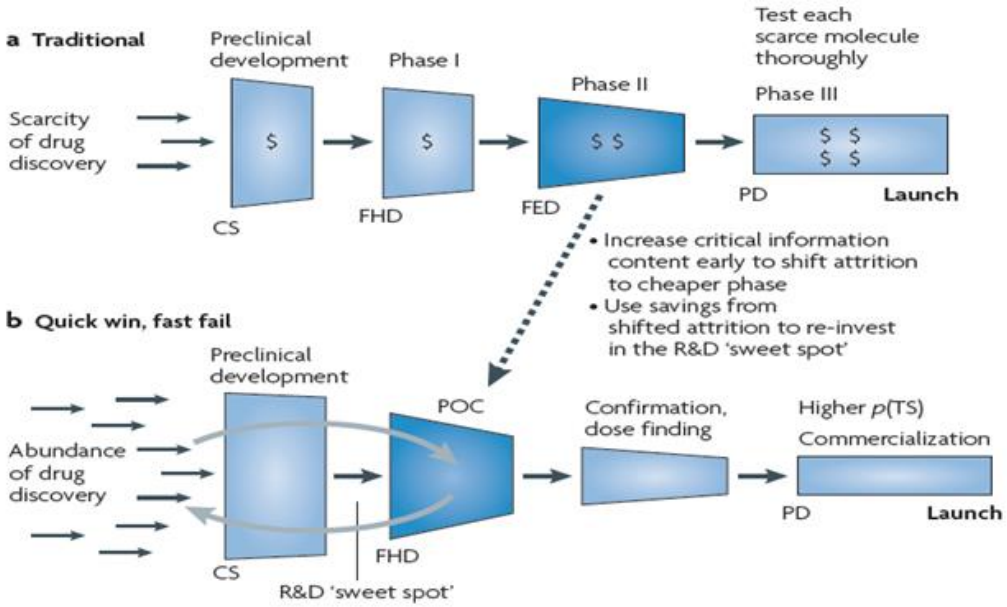

Figure 3. The quick win, fast fail drug development paradigm (obtained from (15))

The direct and indirect benefits of clinical trials have already been studied by PricewaterhouseCoopers and published in a report issued in June, 2013 (4). Clinical trials provide several benefits in the social and economic development of countries, not being Portugal an exception (4). The improvement of health indicators, as clinical investigation comes with innovative, safer and more effective treatments; the early access to advanced treatments, which allow patients the early access to new medicines and therapeutics before their market availability; and the scientific development of investigators and study centres are among the social benefits clinical trials bring to the Portuguese population (4). Regarding the much important economic development, clinical trials help: reducing the public expenditure in treatments and procedures, as the patients' treatment is financed by the study sponsor, replacing the treatment prescribed and paid by the National Health System; improving the commercial scale, by hiring CROs in the Portuguese market, which leads to a significant growth in the exports; and increasing the Portuguese tax revenues, obtained through the direct or indirect taxes generated by clinical trials activities (4).

It is reported that in the European Economic Area (EEA), approximately 4.000 clinical trials are authorised each year (16). From those 4.000 authorised clinical trials, approximately 61% are sponsored by the pharmaceutical industry (16). The remaining 39% are sponsored by non-commercial sponsors, mainly academia (16). The other non-commercial sponsors of clinical trials are foundations, hospitals and research networks (17).

In the specific year of 2015, according to the European Clinical Trials Database (EudraCT), 5526 EudraCT Numbers have been issued (18). This number has been constant throughout the last 5 years, as demonstrated in Figure 4. The EudraCT Numbers do not correlate with submitted clinical trials, as EudraCT Numbers can be issued and the corresponding study never be submitted to regulatory authorities. From those, 79% (4366 clinical trials) had a commercial sponsor; 20%, corresponding to 1005 clinical trials, were sponsored by non-commercial entities; and the remaining 1% did not specified the sponsor in the application (18).

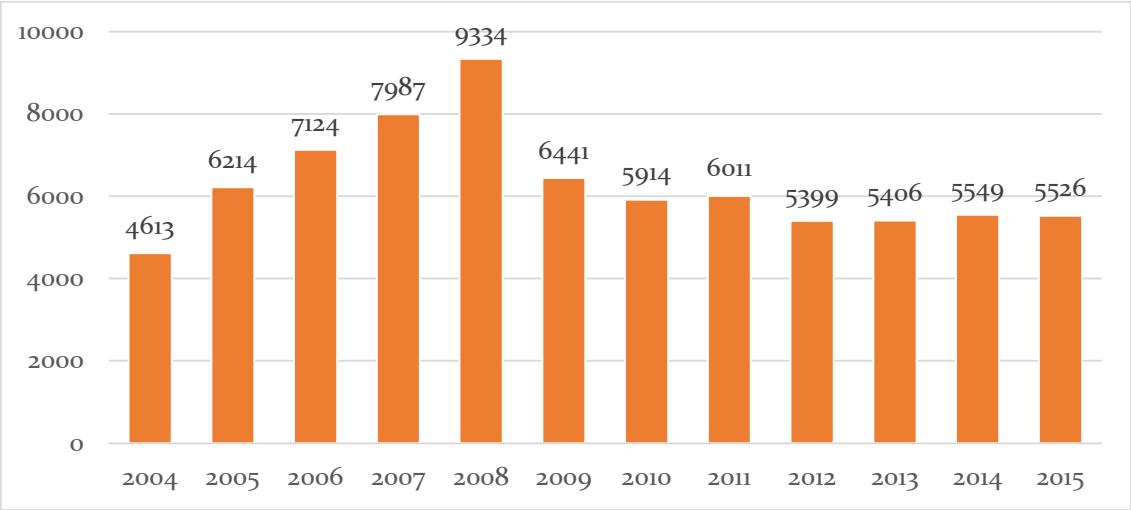

Figure 4. Total of EudraCT Numbers issued from 2004 until 2015 (adapted from (18))

1.3.2. Regulatory Environment

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU) whose main responsibility is the protection and promotion of public and animal health (19,20). It performs such tasks through the evaluation, authorisation and supervision of medicines for human and veterinary use, being, therefore, the most important regulatory authority in the EU for medicinal products (20,21).

The thalidomide disaster in the 1960's was a turning point in the regulatory framework of the EMA, the United States Food and Drug Administration (FDA) and many other medicines agencies (22,23). This tragedy, in part due to the absence of an appropriate regulatory framework in Europe, lead to the creation and establishment of harmonised rules, focusing on a high level of public health protection (22). This disaster was also the trigger for the rigorous medicines' approval and monitoring systems that exist at the FDA today (23).

Developed in the 1950's, thalidomide was a medicine marketed as a mild sleeping pill and advertised as a completely safe product, even for pregnant women (23,24). Later on, in 1960, an Australian obstetrician discovered thalidomide also helped easing morning sickness (23). Prescribing this off-label use of the medicine rapidly became a worldwide trend (23). Thalidomide was then being marketed in 46 countries, having a high demand, especially in the European market (23). It was only in 1961 when that same obstetrician started to associate the intake of thalidomide by pregnant women with the severe birth defects in the babies of those women (23). These findings spread quickly worldwide and, by March of 1962, thalidomide was already banned in most countries where it was being previously sold (23). This great tragedy was avoided in the United States of America, where the drug was prevented of being approved, and consequently sold, due to the lack of data regarding whether thalidomide could cross the placenta or not (23).

Now, after approximately 50 years of the thalidomide disaster, EMA and FDA, the biggest medicines' regulatory authorities worldwide, have evolved and changed many medicine-related policies (22,23). Focusing on EMA, everyone benefits from a strong and cohesive network of CAs in Member States (MSs), the EMA and the European Commission (EC) (22). This relationship brings an harmonisation on how to assess, authorise and monitor medical products, helping to prevent more pharmaceutical disasters (22).

On the light of the worldwide need and desire of harmonisation, in April of 1990 the ICH was created (25). "ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States" (26). Its mission is to make recommendations in order to achieve a superior harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration (26). Ensuring the existence of equal guidelines and requirements, the ICH provided essential tools in order to reduce or even prevent the duplication of testing performed during the research and development of new human medicines (26).

The ICH process has gradually evolved and achieved a great success (25). The Tripartite ICH Guidelines on Quality, Safety and Efficacy were the major hallmark in the ICH's first decade of existence (25). Quality Guidelines brought harmonisation into the conduct of stability studies, through the definition of relevant thresholds for impurities testing, and a more flexible approach to pharmaceutical quality, basing it on Good Manufacturing Practice risk management (27). Safety Guidelines were produced to uncover potential risks like carcino-

genicity, genotoxicity and reprotoxicity (28). In its turn, Efficacy Guidelines were aimed at the design, conduct, safety and reporting of clinical trials (29). The GCP are also part of the Efficacy Guidelines (29). GCP is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials (30). The Multidisciplinary Guidelines were also created in the early years of the ICH (25). They are composed by the cross-cutting topics that do not fit only into one of the Quality, Safety and Efficacy categories (31). The Medical Dictionary for Regulatory Activities (MedDRA) and the Common Technical Document (CTD) are some of the topics which are included in the Multidisciplinary Guidelines (31).

Portugal, being a MS of the EU, is under the jurisdiction of EMA. Taking this information into account, Portugal follows the ICH Guidelines. INFARMED, the Portuguese National Authority of Medicines and Health Products is the main responsible for assuring the fulfilment of those Guidelines. Along with INFARMED, CEIC and CNPD are the authorities who have the responsibility of evaluating and regulating the clinical research in Portugal (6).

INFARMED works under the aegis of the Ministry of Health of the Portuguese Government (32). It is the National Regulatory Authority which evaluates, authorises, regulates and controls human medicines as well as health products, namely medical devices, homeopathic products and cosmetics (32). INFARMED's main objective is to ensure the quality, safety and efficacy of medicines and the quality, safety and performance of health products (32). The Institute performs this tasks in order to avoid the risks of the medicines' use while ensuring adequate standards of public health and consumer's protection (32).

CEIC is an independent entity whose main mission is to guarantee the protection of the rights, safety and well-being of the clinical studies' participants (33). It does so by emitting an ethics opinion about the submitted studies' investigation protocols (33). CEIC only evaluates clinical trials and interventional studies with medical devices for human use (33). Among the parameters evaluated are the benefit-risk of the proposed intervention, the suitability of the investigation team, the feasibility of the study centres and the insurances made for the participants (33).

CNPD is also an independent entity with authority powers (34). It ensures that sensible personal data is handled correctly, assuring the compliance with human rights and legal regulation (34). CNPD authorisation is needed regardless of the study being interventional or observational (34).

The most relevant Portuguese laws regarding clinical research are the following:

- Law No. 21/2014, which is a direct transposition of Directive 2001/20/EC. This law has recently revoked Law No. 46/2004, updating and improving it according to the Portuguese needs;
- Law No. 73/2015, which amended Law No. 21/2014, fixing the conditions in which the CRAs, auditors and inspectors can access the trial subjects' medical registries;
- Law No. 102/2007, which is a transposition of Directive 2005/28/EC. This law establishes the GCP guidelines regarded to the experimental medicines for human use;
- Law No. 67/98. This law establishes the principles and requirements for personal data handling and free movement of personal information. It is a transposition of Directive 95/46/EC;
- Law No. 145/2009. This law transposes Directive 2007/47/EC and establishes the rules to medical devices investigation, manufacture, commercialisation, vigilance and publicity;
- Law No. 189/2008, which establishes the cosmetics and personal care products legal framework.

1.3.3. Clinical Trials in Portugal

In Portugal only clinical trials and other interventional studies, such as cosmetic and medical devices interventional studies, have to be submitted to INFARMED and CEIC. Other studies are usually approved by the local ethics committees. Taking that into account, the only official statistics available are the ones regarding interventional studies.

From 2008, when 146 clinical trials were submitted, Portugal witnessed a decrease until 2011, when only 88 were submitted (35). The number of clinical trials submitted in Portugal have then been increasing since 2012, having in 2015 been submitted 137 studies (35). Among the years (2006-2015) the authorisation rate was around 95% (35). However, the authorisation rate in the specific year of 2015 was of 90% (35). The average decision time has been slightly decreasing over the years. Back in 2007, 45 calendar days was the average time of decision by INFARMED (35). By analysing the data from 2015, we are able to recognise the effects of the new Law No. 21/2014, as the average decision time was of 28 calendar days (19 week

days) (35). According to the 26th article of the same law, INFARMED has a maximum of 30 days to deliberate about the authorisation request (6).

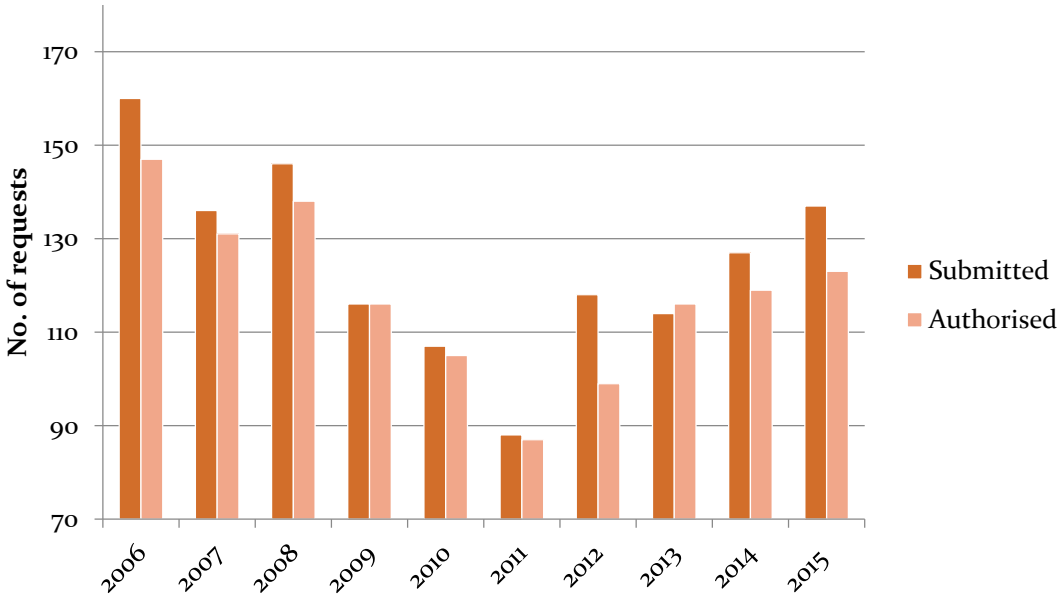

Figure 5. Clinical Trial Authorisation Requests to INFARMED (obtained from (35))

From INFARMED's published clinical trials' statistics, there is also a trend in the clinical trial phases of the submitted authorisation requests. Phase III trials are predominant every year, representing 66% of the requests (35). Phase II trials represent 17% of the clinical trials submitted since 2006 (35). Excluding the years of 2006, 2011, 2013 and 2015, Phase IV clinical trials have always been the third most submitted, accounting for 6% of the requests received by INFARMED (35). The remaining 11% of the clinical trial authorisation requests submitted were of Phase I clinical trials, being 2015 the year with most submitted Phase I clinical trials (35).

The Investigational Medicinal Products (IMPs) are also target of study. They are grouped according to the Anatomical Therapeutic Chemical (ATC) Classification System. The numbers of this studied parameter are a mirror of the population needs nowadays. Medicines for cancer are extremely in demand due to the onset of this disease in our global society. Clinical trials are a clear showcase of this. Requests for clinical trials with antineoplastic and immunomodulating agents have been increasing throughout the years, suffering in 2015 a slight decrease (35). In 2015, 59 clinical trials with those agents have been submitted to INFARMED for authorisation, being the ones with the most requests by a large margin (35). They are then followed by the group of alimentary tract and metabolism, with 17 requests,

and by the antiinfectives for systemic use ATC group, which accounts for 15 requests in a total of 137 clinical trial authorisation requests made to INFARMED last year (35).

The sponsors of the submitted studies have also been target of analysis by INFARMED. Since 2006, the pharmaceutical industry had the biggest share of clinical trials submitted and, consequently, performed (35). From 2006 until 2014, the average percentage of submitted trials by the pharmaceutical industry was of 92 (35). The year of 2015 was no exception. In the last year the academia only accounted for 9% of the clinical trial authorisation requests, whereas the pharmaceutical industry was responsible for the remaining 91% (35).

Regarding to European statistics, on January 1st, 2016, 48.876 studies were ongoing in the EU member countries, according to the clinical trials register (36). Portugal, consistent with the same register, had 887 clinical trials recorded as "ongoing" (36). According to EU statistics, Portugal has a population of around 10,5 million people (37). This means it only has approximately 85 clinical trials per 1 million inhabitants, a number lower than the EU member countries average (140 trials per 1 million inhabitants). In Table 1 this number is compared with countries similar to Portugal in terms of population. Belgium, Hungary and Sweden have around 3 times more clinical trials per inhabitant than Portugal, being Greece the only country to have a similar number.

Table 1. Ongoing Clinical Trials in EU member countries with population between 11,5 and 9,5 million on January 1st, 2016 (adapted from (36))

Country	Ongoing Clinical Trials	Population	Clinical Trials per 1 million inhabitants
Belgium	3039	11.203.992	271
Greece	901	10.992.589	82
Czech Republic	2056	10.512.419	196
Portugal	887	10.427.301	85
Hungary	2275	9.879.000	230
Sweden	2232	9.644.864	231

In the PricewaterhouseCoopers report previously mentioned, Austria is compared to Portugal due to its similar geographic size (Austria and Portugal have 83.879 km² and 92.225 km², respectively) (4,37). Austria only has around 8,5 million inhabitants but manages to have 2.230 ongoing clinical trials at the beginning of 2016 (36). This represents a total of 262 on-

going clinical trials per 1 million inhabitants, more than 3 times when compared with Portugal. This is an indicator on how low the numbers of clinical trials in Portugal are compared with countries with the same size and number of inhabitants.

On the other hand, Portugal has more ongoing clinical trials per inhabitant than Germany, France and Italy, 3 of the 4 most populated countries which belong to the EU. Only the United Kingdom, which has been considered one of the most developed European countries in this sector (4), has a slightly higher number. United Kingdom is also the country which has the highest number of ongoing clinical trials, with 6.035 clinical trials registered as "ongoing" in the clinical trials register website page (36).

Table 2. Ongoing Clinical Trials in the 5 most populated EU member countries on January 1st, 2016 (adapted from (36))

Country	Ongoing Clinical Trials	Population	Clinical Trials per 1 million inhabitants
Germany	5198	80.780.000	64
France	3033	65.856.609	46
United Kingdom	6035	64.308.261	94
Italy	4317	60.782.668	71
Spain	5483	46.507.760	118

2. ON-THE-JOB TRAINING

The internship at DATAMEDICA is, without a doubt, an excellent opportunity to prepare people before integrating the vast clinical research world. The opportunity of being trained and educated in order to meet the demands of the pharmaceutical industry was given to me, being put to good use. The seven and a half months spent at the host company provided the tools for growing as a person and, above all, as a professional of this industry.

Being a CRA involves coordinating the collection, distribution and storage of data obtained during clinical research trials. Submitting the study to the competent authorities, analysing data, creating reports and monitoring individual cases of testing participants are also duties of a CRA. As a small Full Service CRO, DATAMEDICA provided a range of activities beyond the ones usually related with the CRA job. The main activities performed besides the aforementioned ones were data entry, data management, document translation and newsletter creation.

Before describing the internship activities, it is important to mention that prior to receiving any information related to DATAMEDICA's Projects or Clients, every collaborator must sign a Confidentiality Agreement. This agreement concerns all sensitive and confidential information which the collaborator can manage while working at DATAMEDICA. In this report, there will not be mentioned or shared any Clients' names, study's protocol or health products' information, nor any personal data concerning study participants. Despite this, information of public access such as Clinical Trials names may be shared.

2.1. INTRODUCTION TO THE HOST COMPANY WORKFLOW

As previously stated, the internship was started by me on the 1st of June. The three-and-a-half-month period spent at DATAMEDICA before the actual internship had the objective of slowly starting to enter the company workflow.

In order to do that, the company SOPs were read by me, allowing to get a big picture of how procedures in the Scientific Department were done. The purpose of a SOP is to let a person know how to carry out the operations it regards correctly and always in the same manner. Therefore, SOPs are, in my honest opinion, the best way to start understanding the company procedures and fit in its workflow. However, and unfortunately for me, the company SOPs were not up to date. As a result, after getting a full picture of what should be done by me in each particular situation, questions still had to be raised to my superiors in order to understand if the process was supposedly performed as it was being done by me.

After being introduced to the host company workflow and procedures, some protocols of the ongoing clinical studies were given to me by other CRAs. This allowed me to get in touch with a clinical study protocol and to better understand the discussions generated around some studies in the company.

Last but not the least, the Project List sheet was presented to me by the Scientific Manager. The Project List contains all the adjudicated, pending and finished projects of DATAMEDICA. Being in contact with such document allowed me to fully understand the business scope of the company, the ongoing projects and their deadlines. The Project List is, if used correctly and frequently, a good tool for keeping everyone at the company up to date with the status of the projects. It can be time saving, as people no longer have to ask the project managers the status of each project. Instead, they only have to open and read the target project information written in the Project List.

The List was discussed and updated every two weeks in a meeting scheduled by the Scientific Manager. Due to the medical leave of the Scientific Manager in the first months of 2016, those meeting ceased, leading to a gradual disuse of the Project List. By the end of the internship, it was obsolete and not used at all by most of DATAMEDICA's personnel.

2.2. DEVELOPMENT OF STUDY PROPOSALS

Contacts from Portuguese medical societies, national and international pharmaceutical companies and international CROs are a reality every week in a company as DATAMEDICA. Sometimes, the client (the entity who pays for the study, commonly referred to as Sponsor) may require a face-to-face meeting in order to better explain what is intended for the pretended study. Most of the contacts, then, are followed by a confidential proposal.

Study proposals start by describing each company briefly. Then, a background of the disease and medicinal product is written. This allows the team who reads the proposal to understand what the study is about and its therapeutic area. However, the main scope of a proposal is to describe the services which are going to be provided to the sponsor. Among those services are often the protocol and CRF preparation, study submission to the required authorities, monitoring activities and statistical analysis, which are fully explained. A chronogram, essential to the study performance, is also present in a proposal. The chronogram allows getting an overview of the timings of the study. These timings are essential for letting the sponsor knowing when each phase of the study is going to be completed, allowing a better communication between client and CRO. In the end of each proposal comes the study budget. It is usually divided by service, with every hour assigned to each service described, along with its cost.

Being able to read study proposals early on was beneficial. It allowed me to understand the clinical study and the host company deadlines. Both of them were essential for entering the company workflow, as knowing what to do and when to do it was a major gain for both me and DATAMEDICA. When elaborating proposals, a lot of research had to be done by me. Aspects such as the similar studies, similar medicines, specific details of the pathology in hand and so many other details had to be collected from different scientific articles. Not only the proposals were being done, but also new information was being acquired, transforming it in an even more pleasant task.

When concluded, a proposal had to be sent to the Scientific Manager, so that it could be reviewed; to the Chief Financial Officer, in order for the budget to be decided and presented; and to the Chief Executive Officer, who had the task of approving the version and sending it to the client.

2.3. STUDY CONCEPTION

The conception of a clinical study usually begins after the client has adjudicated the proposal. Frequently, a client wants to understand the particularities of a specific population, to support a marketing authorisation for a new medicine or even to study a possible new effect of his existing medicine. In either of these cases, an objective must be defined. It is only after defining that objective that the CRO becomes to develop the study protocol. That is because all the study design, endpoints, number of study centres and so on are based on what is the client's primary objective for the study.

Being part of the team who developed a protocol for an interventional oncology study early on upon entering DATAMEDICA was definitely a challenge. Protocols from oncology and other medical areas had to be read by me in order to better understand how and what had to be written in protocols. Although they were very different among each other, there were some chapters which were common. The study objectives, design, population, procedures, evaluation methodology and monitoring were only some of the major chapters present in all protocols read and in the one which was co-written.

Usually the protocol starts by having an introduction to the disease, the medicinal product (only if it is a study with use of medication) and the purpose of the study. This section helps the investigator who reads the protocol to have a better understanding of the particular disease which is going to be studied. Usually, clinical and non-clinical data that is relevant to the study is written. It should be, however, a brief description. In many protocols it may also be entitled "Background". Developing this kind of introductions was enjoyed by me, as it allowed to better understand some diseases and medical conditions. Even more, it helped to improve the research capabilities as a very selective article search had to be made in platforms like PubMed.

Following the introduction comes the study rationale. In this section, it is supposed to described why the study is going to be developed or why the information which is going to be gathered is important or even needed. The next section was the objectives. This section is generally divided in primary and secondary objectives. Examples of primary objectives are the testing of the clinical efficacy of a drug, the maximum tolerated dose or the assessment of the safety and pharmacokinetics. If it is a non-interventional study, the primary objective might be to study the incidence of a specific disease in the population or even to characterise a specific type of patient. The secondary objectives may be research related to the prima-

ry objective or even central objectives which are not the main objective but are also of interest to the sponsor. In the case of the protocol co-developed by me, these sections were already done by the sponsor of the study, which had previously sent DATAMEDICA and the responsible team a protocol template.

After the objectives, the study design must be explained. The scientific integrity of the trial and the credibility of its data depend substantially on the trial design (1). Therefore, it is common to find in this section a description of the study endpoints, the type/design of the trial (double-blind, placebo-controlled and parallel design, for example), a schematic diagram of its procedures and stages and also a description of the measures taken to minimize or even avoid bias (randomisation and/or blinding). Also in the study design chapter are the expected duration of the subjects' participation and the identification of the data to be recorded directly on the CRFs. Formerly, the target subject population topic is developed. Subject inclusion and exclusion criteria are vital subchapters, as well as the subjects' withdrawal criteria.

As the developed protocol was for an interventional study without medication, chapters as the treatment of subjects, assessment of efficacy and assessment of safety were skipped. However, if it was a protocol for an interventional study with medication or a medical device, those chapters would have to be described, as they are of major importance. The following chapters, such as the ethical conduct of the study and the sponsor's study management were already written. They were probably completed because they are a standard for every interventional study without involved medication the sponsor performs.

The final chapters were co-written along DATAMEDICA's Data Manager and Medical Statistician, as their focuses were exactly the Data Management, Statistical Methods and Sample Size Determination. These chapters were initially done by him, with the Portuguese translation to English being done by me. Translating these chapters of the protocol was of critical importance, as new notions of Biostatistics were learned by me.

Right after the protocol, the CRF is the other document of great importance in the study conception. The CRF is the instrument used by the sponsor of the study to collect data from each participating subject. All the information gathered and registered by the investigator is documented in the CRF. Despite being where the entire participant's information is gathered, the CRF does not contain the participant's name or any self-identification number, such as the social security or identity card number. Instead, a study number is attributed to

each participant. By doing this, it is completely guaranteed the data is anonymized before being sent to the sponsor.

A CRF can be a paper CRF or an electronic CRF (eCRF). In the beginning of clinical research all CRFs were made on paper. However, and following the technology and clinical research's evolution, there is a changing trend regarding CRFs. In the present day only a few clinical studies still use paper CRFs. The new trend is using eCRFs, which comes with many advantages: they are faster and more efficient; all data is highly secured compared to the CRFs on paper; and they are environmentally friendly, as no paper has to be wasted in the forms.

No CRF was developed by me during the internship at the host company. However, an eCRF validation was done by me. The study in hand was related with a rare disease and was sponsored by a Portuguese Medical Society. The validation of an eCRF consists on checking if there is a homogeneous structure, a logical consistency and protocol compliance. Only by doing this activity can the data be accurate and complete. Firstly, the structure was evaluated by me. It had to perfectly match the instructions given to the programmer who developed the eCRF. After assessing its structure, a battery of tests was done to assure the form was consistent. All fields were tested with unusual or even wrong data. Fields where numbers were supposed to be were submitted with letters. Extreme values were tested (e.g., the test was done when the study participant had 300 years old). After guaranteeing only meaningful data could be introduced and submitted, the questions branching was verified. Branching is when a specific answer to a certain question leads to a particular page or even opens a new question in the form. After assuring the platform was compliant with the protocol, the eCRF validation was marked as finished by me.

While developing and validating CRFs and eCRFs, one particular detail must be taken into account: they must be user-friendly. A CRF, electronic or in paper format, must be easy, intuitive and natural to use. Otherwise, the investigator is going to feel confused or even lost in it. During my internship, one particular eCRF was considered by me not to be user-friendly. Its design was not the best and completing it was difficult, as many questions had to be answered in the same page. Moreover, all the fields in the eCRF had to be completed before being submitted, not leaving the option of starting in one day and finishing to write the information the day after, being a major hurdle when the investigator was short on time.

2.4. STUDY SUBMISSION

The study submission is one of the vital phases a clinical study goes through. It is during its submission and posterior evaluation from the competent authorities that the sponsor gets to know if the study is able to keep moving forward. The authorities to whom the CRO or Sponsor submits the study depends on its type: interventional or non-interventional.

An interventional study must firstly have a EudraCT number. In order to have a EudraCT number, the study registration must be made in EMA's specific (eudract.ema.europa.eu). To do so, some information regarding the applicant, sponsor and protocol are required, such as:

- Applicant's organisation name, city and country;
- Sponsor's Protocol code number;
- Name and e-mail address of the person to whom the EudraCT number will be sent;
- The MSs where the study is, *a priori*, going to be conducted;
- Whether the Clinical Trial is contained in a Paediatric Investigation Plan;
- Whether the Clinical Trial will be performed in a third country (outside of the EU/European Economic Area).

After the submission of the EudraCT Number form, an email will be received by the person appointed before. The format of the EudraCT no. is YYYY-NNNNNN-CC, where: YYYY corresponds to the year in which the number is issued; NNNNNN is a sequential number; and CC is a check digit (38).

Once the study has a EudraCT number, the study must be submitted to the CNPD. The CNPD will assess the study variables at stake. The processing and distribution of the study's sensitive and personal data will be the scope of the evaluation. The application, made in the CNPD website (www.cnpd.pt), has a cost of 150,00€ and must include the following information:

- Identity and information of the study's sponsor;
- Identity and contacts of the person or entity responsible for all the data management;

- Type of data collected (e.g. philosophical convictions; ethnicity; private life; health, genetic or sexual life data) and how it is going to be obtained (directly or indirectly);
- If the data is going to be transmitted to 3rd parties or to a country outside the EU/EEA;
- Study documentation such as the protocol synopsis, ICF, Patient Information Sheet (PIS) and list of the study variables.

At DATAMEDICA, interventional studies are only submitted to INFARMED or CEIC after obtaining the CNPD's authorisation. However, this authorisation is not among INFARMED's requirements for submitting an interventional study.

According to the law no. 21/2014, CNPD has 30 days to authorise or to not authorise the data management process. This is a scenario that, during the seven and a half months spent in the host company, was not a reality. Every CNPD process took around 3 to 4 months to be authorised or to have questions raised. One particular process, regarding one study with questionnaires, was submitted in the month of June 2014 and, in the end of April 2016, was still waiting for CNPD's reply, even with biweekly phone calls reminding CNPD about this situation.

After having CNPD's authorisation, the study is submitted to INFARMED in order to obtain its authorisation. INFARMED's authorisation is vital for performing an interventional clinical study in Portugal. Submissions to INFARMED for an interventional clinical study with a medicine for human use have a cost of 1.000,00€. They must follow the requirements present in the "Instructions for applicants" from July 27th, 2015, featured in INFARMED's website and be performed according to the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (CT1)" from October, 2005. Being all documents required important and essential to have a positive authorisation, the ones most relevant according to my opinion are the following:

- Signed Clinical Trial Protocol (signatures from the sponsor, coordinating investigator and principal investigators);
- Investigator's Brochure, which contains relevant data of the medicine gathered during preclinical and other clinical studies in human subjects, or the Summary of

Product Characteristics, which is developed before the medicinal product being marketed and that summarizes its proprieties;

- IMP Dossier, which includes summaries of information related to the quality, manufacture and control of any IMP and data from non-clinical and clinical studies;
- List of ongoing interventional clinical studies with the same IMP;
- Clinical Trial Application (CTA), in XML format. The CTA has 10 sections which go from Trial, Sponsor, Applicant and IMP Identification to Population of Trial Subjects and CA/Ethics Committee Information.

All the documentation present in INFARMED's "Instructions to applicants" must be saved on a CD-ROM. Every document has a specific location, which is also explained in the "Instruction to applicants" aforementioned. If the study is not an interventional clinical study with a medicine for human use (clinical trial), the submission is slightly different. For example, if the sponsor intends to submit an authorisation request for an interventional study with a class III, IIb or IIa medical device, new folders and documents must be included. Those folders must contain efficacy, quality, safety and the CE marking documents.

Right after INFARMED's submission, it is important to submit the study to CEIC. It is requested to CEIC an opinion instead of an authorisation. The positive ethics opinion of CEIC is also essential in order to perform an interventional clinical study. According to CEIC, the objective of the clinical trial is to obtain knowledge which can become useful for treating the patient's disease or future patients. The patient cannot face a clinical trial as a solution for easily accessing a medicine. There has to be some altruism by the patient when entering a clinical trial. This is called therapeutic misconception, and is essential according to CEIC.

The request must comply with the "Guidelines to observe by applicants about the format and content of the ethics opinion request to CEIC for performing a clinical trial with medicines for human use, notification/request of alterations, adverse events notification and end of trial declaration" from June, 2005. However, the content and organisation of the CD-ROM to be submitted with all the information regarding the submission has been changed. Since October 5th, 2015, there is a new CD-ROM organisation, made to ease the documents' organisation for the submission process. In my opinion, the most relevant documents present in the application are the following:

- Experimental medicine circuit;

- ICF and PIS;
- Patient recruitment method;
- Insurance policy for the interventional clinical study;
- Financial contracts to establish with the study centres.

During both evaluation processes, the entities may raise questions about any documentation or process regarding the study. If that occurs, the CRA responsible for the study must inform the Sponsor of such event. The reply to INFARMED or CEIC must be made as soon as possible in order not to delay the approval from both entities. INFARMED and CEIC have both 30 days to deliberate about the authorisation/opinion request, according to law no. 21/2014. And, unlikely CNPD, these entities follow the law and perform their duties in the specified time.

After INFARMED and CNPD's authorisation and CEIC's positive opinion being obtained, the CRA must submit the interventional clinical study to the ABs of the centres where the sponsor desires to perform the study. This is the final authorisation needed in order to successfully perform a clinical trial in Portugal. Every hospital has its own requirements. However, almost every hospitals and hospital centres require these documents:

- Study Protocol;
- ICF and PIS;
- CRF;
- Authorisation from the Department's Director;
- Principal Investigator's Curriculum Vitae;
- Financial Contract between the Sponsor and the Hospital.

The financial contract is one of the most controversial and difficult documents to be finalised. Firstly, every centre has its own requirements regarding financial contracts. The values involved can be discussed in two ways: the first involves paying the study centre an amount of money for each patient included; in the second, a global value is attributed to the centre, not having any special goal to achieve. Moreover, some centres have higher percentages assigned to the clinical research funds, while others have a greater percentage allotted to the clinical research team. This is a hurdle to overcome when negotiating the contracts, as

the sponsor has to pay more if there is a desire for each investigator receiving exactly the same amount for the work being done.

The host company did not have a template for financial contracts at my arrival. However, after one study whose sponsor did not also have a template, the R&D Officer of DATAMEDICA made one for the company. The template was revised by me and was further used in the aforementioned study and in another study which required a financial contract. The document created had the following topics: scope of the study; monitoring by the sponsor or the other authorised organisations; non-disclosure of the results; data privacy; intellectual property and publishing; financial provisions; and contract period, among other topics. As it is a legal document, it must be revised by lawyers of both sponsor and study centre. This was, during my presence in the host company, a major delaying aspect. The legal team from the sponsor always wanted to discard some responsibilities, while the one from the study centre desired to write every single aspect they believed to be necessary in the contract. Being revised multiple times delayed the signing of the contract, and, consequently, the start of the study in the centre.

Having submitted approximately a dozen studies to ABs during the internship for a particular study in the cardiology area, the Scientific Manager of DATAMEDICA asked me to make a document with the Hospitals' requirements. In that document, all the requirements from the different Portuguese Hospitals (around 30) where the aforementioned study was submitted were compiled by me. The result was a database where all documents needed to submit a study in specific hospitals were registered. This allows to decrease the time since the authorisation from INFARMED and positive CEIC's opinion is given until the study is submitted to the Hospitals' ABs, as all needed documents are already catalogued.

After having the AB's authorisation, an interventional clinical study can be performed in a study centre. However, the study can only start after the team having received appropriate training on the study protocol and CRF involved. These subjects are all part of a Site Initiation Visit (SIV), which is going to be explained in the next chapter.

In some cases, during the study period, clinical trial amendments must be done. An amendment is an alteration done by the sponsor to the protocol, IMP Dossier, Investigator's Brochure (IB) or any other document submitted to the regulatory authorities and/or study centres. These amendments arise from new scientific information which has come to light or because, after analysing some collected data, the sponsor believes it is better to reformu-

late a specific study part. The performance of amendments regarding the clinical study after its beginning is allowed according to the European Regulations and Portuguese Laws. Amendments can be classified as substantial or as non-substantial. Substantial amendments have a significant impact on the safety of the participants, on the scientific value of the study, on the conduction/management of the study or on the quality/safety of the IMP used in the study. On the other hand, amendments are classified as non-substantial when they do not meet any of the aforementioned criteria.

Both types of amendments were encountered by me during the internship at the host company. My major task regarding amendments was writing the notification letter which was going to be submitted to both CEIC and INFARMED. It made me realise that even well thought and prepared studies can be target of alterations due to clinical study related events.

The submission of non-interventional studies is slightly different, as shown in Table 3. These type of studies do not have to be submitted to INFARMED nor CEIC. Instead, they are submitted to the Hospital's AB and Health Ethics Committee. Usually, the Health Ethics Committee is the Hospital Ethics Committee. However, if the hospital does not have an Ethics Committee, it has to designate one to evaluate these studies.

Table 3. Approving Entities regarding the different type of studies

	Regulatory Authority	**Ethics Committee**
Interventional Study	INFARMED	CEIC
Non-interventional Study	Hospital's Administration Board	Hospital or Local's Ethics Committee

The submission process starts by having to obtain the same CNPD's authorisation in order to collect and manage the desired data. Subsequently, the study has to be submitted to the Hospital's AB and Ethics Committee. Sometimes the study even has to be submitted to the Hospital's Clinical Committee in order to be appraised. The documentation needed by the hospital entities to evaluate the study is the same which is required by the hospitals' AB to assess interventional clinical studies. In most of the Portuguese hospitals the AB only deliberates on the study after a positive opinion has been given by the Ethics Committee. After

having both AB's authorisation and Ethics Committee positive opinion, the study is allowed to be started in the Hospital.

Some hospitals, though, require a study contract between the sponsor and the centre for the study to effectively start. The contract is similar to the one described before in the submission of interventional clinical studies. The main difference is not having financial benefits to the investigator nor to the centre. So, in most of the cases, that clause is removed from the contract. When it is not removed, which was once the case, it explicitly stated the clinical study, as a result of being non-interventional, did not have any type of funding involved.

Before starting the internship at the host company, believed by me was that positive opinions from CEIC were more difficult to be obtained than the ones from Hospital Ethics Committees. After submitting a non-interventional clinical study in several hospitals, my mindset completely changed. There is nothing more difficult than obtaining a green light to perform clinical studies from Ethic Committees in some Portuguese hospitals. This happens because of numerous aspects: firstly, the Ethics Committees in most of the hospitals do not meet regularly but only when they have "a considerable amount of processes to analyse"; secondly, there may be a misunderstanding of the Committees' members, who might still consider that clinical trials do no good to the population, becoming then an insurmountable blocking force, not allowing any study to be performed; and last but not the least, from being given a positive opinion in a meeting until the process is redacted by the responsible reporter goes an incomprehensively big amount of time. All these aspects only contribute, in my opinion, to a decrease in the non-interventional clinical studies performed in Portugal.

2.5. STUDY MONITORING

In normal circumstances, study monitoring occupies most of the time of a CRA. It is not by chance that CRA are frequently dubbed "Monitors" instead of being called "Clinical Research Associates". It is estimated that 41% of a CRA's time is spent during on-site monitoring activities (39). Beyond that, an extraordinary 20% of their time is spent traveling to and from study centres (39). Centre visits can be divided in 5 different types: Pre-SIVs, SIVs, Monitoring visits, Pharmacy visits and COVs.

2.5.1. Pre-Study Initiation Visits

Pre-SIVs, also called Qualification Visits, are performed in order to review the adequacy of the site, the training and experience of the study staff, the access to the right patient population and the site's interest in the study. During the internship at DATAMEDICA a Pre-SIV was done with my presence. During this visit, the Lead CRA explained the team the study details, giving special attention to its inclusion and exclusion criteria. Those aspects were explained with more detail so that the Lead CRA was able to really understand if the centre was capable of recruiting the needed number of participants. Training in ICH-GCP was also given to the investigators, who had no knowledge of its content. This training was requested by the Sponsor.

This ICH-GCP training was developed by DATAMEDICA. The Lead CRA presented it, based on the entire ICH-GCP document but specially focused on the Investigator's duties and responsibilities during the interventional clinical study. ICF, CRFs, Severe Adverse Events (SAEs) and their reporting, and premature suspension of a trial were also mentioned by the Lead CRA. By giving this training, investigators became aware of what and how they had to execute certain tasks so that the study was performed according to the ICH-GCP. An online exam was mandatory for issuing a certificate. The exam was made by me, with a simple but effective online platform. Investigators had to get a score of 90% or higher in order to obtain DATAMEDICA's ICH-GCP certificate. Almost all the investigators managed to obtain such score on their first attempt.

Although not always performed, a Pre-SIV is an interesting visit to execute, allowing to understand how enthusiastic and interested the investigators and/or staff are. This may be predicting on how the study is going to develop in that specific centre, as focused and fascinated teams tend to have the best results and less protocol deviations.

2.5.2. Site Initiation Visits

SIVs are the first or second contact with the investigators, in case a Pre-SIV was completed before. SIVs are performed right before the study being activated for enrolment by the Sponsor. This visit allows the CRA to give a deep and adequate training on the study protocol. The review of the CRF must also be done with the investigators, as well as the study file organisation, in order for it to be the same throughout the different study centres. The SIV also lets the CRA to ensure the investigator understands his/her responsibilities towards the study. This is of utmost importance, as the investigator has to perform his/her duties adequately so that the study can go on without protocol deviations. These visits only occur after the site has the approval from all the regulatory entities.

During the internship at DATAMEDICA, two types of SIVs were organised. Some SIVs were performed the most typical way, with the responsible CRA organising a meeting with all staff from the centre. The other type of SIVs was performed as an investigators' meeting. This meeting allows gathering a large number of investigators in the same place. It is a practical way of conducting many site initiation visits at once. Both types have their positive and negative sides. On the one hand, the first type allows giving a more personal explanation of all studies, despite having a larger cost burden. On the other hand, the investigators' meeting lets the CRA performing almost or even all SIVs at the same time, with the negative side of not being able to comprehend if all the participants had, in fact, understood all the information transmitted. Having witnessed both types of SIVs, separate SIVs are in my honest opinion more valuable. That is because the investigators and study staff feels more comfortable and have more time to ask every kind of questions related with the study.

2.5.3. Monitoring and Pharmacy Visits

With the study being performed, monitoring visits to the centres must be scheduled. Monitoring visits are important to evaluate how the study is being conducted but also to perform Source Data Verification (SDV). "SDV, commonly known as «transcription checking», is the process by which data within the CRF or other data collection systems are compared to the original source of information (and vice-versa) to confirm that the data were transcribed accurately" (40). Examples of source documents are the participant's medical files, a laboratory report or a patient's diary, between many others. The duration and periodicity of the monitoring visits are agreed when the sponsor contacts the CRO to perform such tasks.

They can occur every month or only once a year, for example. Their duration is also variable. Depending on the study, monitoring visits can last one day or even a week, depending on how much information is going to be verified. One of the most important Clinical Trials ongoing at the host company had monitoring visits every 3 months, each lasting for 3 days. Accompanying the CRA on a monitoring visit made me understand the tasks a CRA has to perform before, during and after each visit.

Apart from performing SDV, a CRA must also make sure all the study team is motivated and focused on the study. This is also a capital task during monitoring visits, as without a motivated team the study is not going to perform its recruitment as it is supposed, leading sometimes to sub-recruiting. This lack of recruitment is not good for both CRO and Sponsor. While the first one may be accused of performing a deficient feasibility of the centre, the latter may not have enough data to perform a valid and consistent statistical analysis of the data, leading to both waste of time and money.

Before performing a monitoring visit, a CRA must prepare it, as done a couple of times by me. Firstly, an identification of what was done during the previous visit was made. Afterwards, the monitoring visit report was consulted in order to check if any task was left uncompleted during the last monitoring visit. If any issue was pending from the last visit, it would become one of the top priorities for the next monitoring visit. If electronic, the CRF would also be verified. This allows to quickly knowing how many patient visits were not monitored since the last visit. It also lets the CRA check for any raised query which was not yet resolved. A query is an inconsistency or mismatch between the source document and the CRF. In the end of all verifications, a checklist of everything that should be done by me during the monitoring visit was done, in order not to forget any issue or relevant aspect. All in-house project files should also be updated to ensure all the documentation is properly stored, even the correspondence between CRA and study centre or study coordinator.

My first interventional clinical study accompanying a CRA was done in a urology medical device interventional study. It was only performed in one hospital in Lisbon, which made travel easy and not time consuming. The monitoring visits only lasted for one day and were done every 4 months. They had that much time between them because the visits were supposedly done every time 20 new patients were recruited. Not having a monitoring manual, which usually explains the tasks to be performed during the monitoring visit and SDV percentages, the Lead CRA decided to perform a 100% SDV. This means every single entry in

the CRF must be checked and confirmed as being a perfect match with the source document. It is a time consuming process but, in the end, all the data collected during the study is precise and accurate, resulting in consistent and valid outcomes.

When the CRA responsible for the study left DATAMEDICA in the end of February, the project became my responsibility. A handover of the project was then done, as every single aspect from the clinical study should be explained to the following CRA. A good handover is the key for the process changing "hands" and continuing being performed without any major mishaps or setbacks. That process was not complex, as two monitoring visits were already performed along the CRA. A handover report was prepared by me, stating all the information the former CRA explained to me during the handover meeting. As every project is different and the information to be transmitted differs in each project, DATAMEDICA has no "Project Handover" template. This means every time a report of this kind is prepared, it must be made from scratch.

It was learned by me that a good preparation of a monitoring visit is critical. In my last co-monitoring visit in DATAMEDICA, performed in a Porto centre, the responsible CRA did a superb preparation of the visit, making sure everything was also acquainted by me. This allowed us to reach both pharmacy and study centre and "quickly" pinpoint what needed to be corrected as well as to correctly archive or collect the necessary documents. Despite all the efforts and preparation, the study coordinator for the study did not have the time or opportunity to correct all the CRF pages, taking the monitoring team a lot more time than expected. Moreover, the CRF pages needed a thorough revision, which also contributed for a delay in the monitoring visits. In the light of the new rules of the centre, the monitoring visits were shortened. As a result, these delays, which formerly did not cause any setbacks, can now be harmful to the correct performance of the monitoring visit.

During a periodic monitoring visit, not only the SDV and document archival are made. Medication accountability and destruction are also activities to be performed. This is done while visiting the pharmacy from the study centre. Study medication's accountability is an essential task, allowing the CRA to verify the patients' compliance. Only by doing this can the clinical data integrity be assured and the quality and acceptability of the study be guaranteed. Patient's noncompliance is also a major issue, as it can compromise their safety due to lack or even excess of medication. This task is accomplished by verifying the dispensing of medication and counting the pills and/or medication bottles which were used and un-

used. The confirmation of the batch numbers are a step always to be done during this task. In the end, the CRA's verification must match the records from the pharmacy. This is also a process to be made before returning or disposing any study medication. In some cases, the cartoons which contained the medicinal products must also be sent back to the sponsor (or the entity which has been designated for such purpose).

For disposing or sending to the sponsor the study medication and/or cartons, the accountability must be firstly made. After confirming the medication which entered the study pharmacy is a correct match of the one which was used by the patients and is left, a form must be filled. In that form, the medication name must be written, along with its batch number and expiry date. Every carton, bottle or even pill must be registered in the accountability form. After doing that, the sponsor instructions must be followed, often resulting in a contact with a transporting company to perform the transportation of the container which encloses the medication and/or cartons. In some cases, if the items are to be destroyed by an external company, the contact is made with that company, which usually performs both transport and destruction.

Keeping track of the medication stock is also important for a CRA. Depending on the study and sponsor's instructions, the CRA may request medication to be sent to the pharmacy. It is an activity of capital importance, as no one at the study centre or the CRO wants a patient to miss his/her treatment due to lack of attention by the monitoring team. This is usually a task performed by an experienced CRA or the Project Manager, reason why it was only witnessed but never performed by me during the internship.

During the centre's pharmacy visit, the medicines' storage conditions must also be verified. All the medication of the study must be in a locked area, dully secured, with temperature and humidity control. Humidity and temperature must be continuously checked and the pharmacies must have a log of how these factors varied along the day because medicines' stability is affected by both these factors. In some centres, the log is electronic, being registered continuously by a device. The information on the device can then be downloaded directly to a computer. This results in a user-friendly graph, which can be easily analysed by the CRA. If any deviation from the humidity or temperature desired parameters is registered, the study medication must be sent to quarantine. In this scenario, the sponsor is contacted and can decide not to use that medication. Damaged cartoons and missing or wrong patient information leaflets are also a motive for sending medicines to quarantine.

2.5.4. Close-Out Visits

The CRA also has to perform a COV when the study has been completed at a centre. They can be performed two ways, being the first more common: an on-site visit, combined with a final periodic monitoring visit; or as a telephone call, stating the end of the clinical study in the centre. During this type of visits, plans for record retention are discussed and a final review of the study file documents is performed. One of the most important things to be done is to establish timelines for the completion of outstanding case report forms and queries, as no missing or mismatching data must be left overlooked.

During a COV, all site documents must also be prepared for archival. This is synonym of collecting all the originals in order to be sent to the sponsor and also to box every dossier and document for being stored in the hospital archive for the determined time period. The Investigator File must be free from clips, staples and post-its, and duplicated documents must also be removed. Furthermore, File Notes must be added to any section present on the index which does not have any document. These File Notes (or Note to File) are frequently used to document the reason for missing, delayed or erroneous documents in the Investigator File and to explain protocol deviation or investigator site practices which are different from the explained in the protocol or guideline.

The pharmacy must also be visited in order to account for the remaining study medication. It must be either returned or destroyed, depending on the sponsor's information. The Pharmacy File must also be prepared for archival, the same way the Investigator File mentioned above was. Usually both those Files are archived together.

2.5.5. Visit Reports

At the end of each of the aforementioned visits, a report must be done. The report must be done as soon as possible in order not to forget any information that came to light during the visit to the centre. According to DATAMEDICA's SOPs, the visit report has a specific template to be followed and must be completed within 10 week days from the visit. However, if demanded by the sponsor, the CRA must follow its SOPs. In this case, there may be a specific template and a different deadline for delivering the first report version.

The report must identify the study, the visit date, the centre where the visit occurs and the people who were at the visit. After that, a resume of the study status on that specific centre must be done, specially focused on the number of patients screened, recruited, completed

and withdrawn. These numbers are of great value when the sponsor tries to verify if the centre is approaching the target recruitment number. The report must also address the following topics:

- Study Team – change in staff, new members' training and delegation of functions, between others;
- Investigational Products – its storage, quantity, usage and expiry date, for example;
- CRF – accurate record of data, consistency with the source documents, missing laboratory analysis' results and use of concomitant medication, among other subtopics;
- Protocol Deviations, if any;
- Adverse Events (AEs) and SAEs' report;
- Adequate Study File's maintenance and archival.

Having finished writing a visit report, it must be sent to the Sponsor for being revised. After the revision by the Sponsor questions can be raised. These questions can be related with several aspects. After being revised and approved by the sponsor, the same report must be sent to the study centre, accompanied by a follow-up letter. The letter summarises the visit and describes all the significant findings or required actions to be performed, if any. During the internship only two visit reports were made by me. The first one was developed following a monitoring visit to the only hospital where the aforementioned medical device study took place. The template used was DATAMEDICA's one, making the writing of the report easy. This was because it consisted on a template studied upon entering the host company, as it was an integral part of the company SOPs. The monitoring visit report was afterwards submitted to the sponsor and sent to the investigational team, along with some remarks.

Some particular studies have online platforms provided by the sponsor to write the monitoring visit reports. In these cases, the fields are filled with the information regarding the study. The first visit report "written" on an online platform was regarding an oncology study monitoring visit co-monitored by me. The report was more appealing and easier to do, as some fields were interactive and somehow better focused on the monitoring visit than DATAMEDICA's template. This was perfectly normal in my opinion, as international companies have already had several studies for perfecting their monitoring visits report forms.

2.5.6. Queries' Management

In my point of view, queries can be broadly classified in two types. The first type of queries is when someone fills the CRF with information that is not possible of being correct. In example, if a patient makes the 1st, 2nd and 3rd visit in, respectively, 2015, 2016 and 2015, something is probably wrong. The second type of queries is when, after performing SDV to the CRF, a value was deemed wrong because of not being the same as the Source Document's value. It is, basically, a transcription error that is easily spotted during monitoring visits. However, all queries are handled equally and with the study coordinator or person responsible for filling the CRF.

On the other hand, the existence of two types of CRFs (paper and electronic format) does make the management of queries different. If paper CRFs only allow the CRA to check for queries on the study centre, the same does not apply for eCRFs. During the internship in the host company, both types of CRFs were verified by me. And, personally, managing eCRFs is an easier task because there are no handwriting issues, the platforms usually are user-friendly and the aforementioned first type of queries are easily spotted and managed. Those queries can be even automatically raised by the platform if it is properly made and validated. One particular international study in the cardiology area with over 100 study centres just in Portugal was a challenge to manage. The eCRF had an international team of data managers responsible of raising queries. In the end of the study, over 500 queries were raised by that team, turning my and the responsible CRA's work difficult, as every investigator had to be contacted in order to resolve those queries. It was an overall good experience because it made me realise that from one moment to another several queries can be raised by the data management team. Not only that, this event helped me understand a CRA has more work than just visiting centres in order to monitor their activities and CRFs.

2.5.7. Study File Management

The Study Master File (SMF) is a document which contains all general documents of the study, not site specific, as well as all the correspondence from and to the Sponsor. Those documents are arranged according to the SMF index, which in most of the cases is DATAMEDICA's one. This file must be updated throughout the study, being this update responsibility of the study's CRA. The frequency of the update is related with the study complexity. The SMF also has to be returned to the Sponsor after the study close out, if

agreed between both entities. In some cases, international CROs which do not have presence in Portugal hire local CROs to implement and monitor studies. In these particular cases, the SMF is hold in the international CRO's facilities. This implies sending regularly documents to the international CRO in order for the SMF being up-to-date.

During the internship the index of the SMF was updated by me, following comments and tips from my colleagues. The changes made were then mirrored in the folders' organisation in DATAMEDICA's server. Basically, the server's folder template for new projects was updated in order for the search for documents becoming easier. Having the same organisation in both paper and electronic format saves time when documents are archived in the SMF, as the location is the same as the server's. It was at first a difficult change, as every person at the company was used to the older server's folder organisation. But, after some time, it became natural and more productive.

For the archiving of site specific documents from each investigational site, and Investigator Study File has to be created by DATAMEDICA but updated by the investigator. This File must be available to the CRA during monitoring visits for the files to be checked. There is also a Pharmacy File, which contains the pharmacy site specific study documents. As well as the Investigator Study File, the Pharmacy File must be updated by the pharmacist responsible for the study and be available to the CRA during the visits to the centre's pharmacy. Both Files have their own index, different from the SMF and adapted to the needs of each File.

2.6. OTHER INTERNSHIP ACTIVITIES

During the internship several non-CRA related activities were performed by me. This happened because DATAMEDICA, being a small company, allows the same person to perform a broad spectrum of activities. This is enriching because it allows the trainees to develop various skills in different areas, allowing them, and in this case me, to become multidisciplinary. Among the different activities performed, the more relevant ones were the performance of Data Entry, elaboration of Study Newsletters, translation of Study Document and creation of Certificates.

2.6.1. Data Entry

Data entry was the very first activity performed by me upon entering DATAMEDICA. It is a fairly basic activity, only requiring perception and focus during its performance. The objective is to copy (or entry) data of paper CRFs into a spreadsheet or other desired document. It is done in order to allow the Statistician to work the data and eventually perform a statistical analysis. The main issue in performing data entry is the hand writing calligraphy. It made my task harder as some entries in the CRF were not discernible. In those cases, help was requested by me to other people in DATAMEDICA who had more experience in doing this activity.

2.6.2. Study Newsletters

The need to create a Study Newsletter emerged when the coordinating investigator of a rare disease non-interventional study desired to inform and motivate all the investigators involved in the study. The best way to do so was to create a newsletter containing information regarding the study. It was created from scratch by me using Microsoft Publisher 2016, a Microsoft Office program intended to create posters, letters and leaflets, among others.

At first, other studies' newsletters were observed and studied by me in order to understand what was supposed to be contained in them. Afterwards, the design was thoroughly though until reaching the final version, which was complimented by everyone at the host company. While being simplistic and clean, the design was attractive and the information allowed creating some "good competition" between the centres and investigators. This was because there was a horizontal bar graphic which mentioned how many patients the centres had already recruited. One aspect which was present in many other newsletters observed by me

was the expected recruiting vs the real recruiting. This kind of graphic allows the reader to understand if the centres are recruiting at a rate comparable to the originally anticipated by the sponsor. Although the studies for which I had to make newsletters had a target recruitment number, this type of information was neither relevant nor required by the sponsor, as the study timings could be extended in order to recruit the desired number of patients.

2.6.3. Translation of Study Documents

During the development clinical studies, many documents are issued by the regulatory authorities. In international clinical studies, those documents have to be translated from Portuguese to English in order to be sent to the international company. As hiring people or companies who issue certificates of translation is expensive, the international sponsor asked DATAMEDICA to translate the documents. Having a Certificate of Proficiency in English put me in a privileged position to perform these tasks. Therefore, all the document translation which had to be done since my arrival at the host company was performed by me.

The most translated documents were from CEIC and INFARMED, as interventional clinical studies require a lot of communication with those regulatory authorities. At first the biggest difficulty was to translate the legal-related words, as they were unfamiliar vocabulary. After getting the hang of it, translations became a rather easy task. The translations the sponsor required to be certified were back translated by the Scientific Manager in order to verify if they had been correctly performed. Afterwards, DATAMEDICA's certificate of translation was issued, being signed by the translator and the reviser. Some ICF and PIS were also translated by me, in the light of an audit which was in the verge of being performed in the central coordinating centre of an oncology study, which was in the United Kingdom.

Being able to perform these translations made me improve my translating skills and, simultaneously, understand and realize which information was present in several study and regulatory authorities' documents. Developing these activities may become relevant if at any time of my career there is a desire to perform the CRA job on an English-speaking country.

2.6.4. Trainings, Evaluation Register and Certificates

As a result of a new DATAMEDICA's policy, many training actions were performed in the company along the year. Those trainings were performed by colleagues who attended congresses and meetings regarding important themes. Furthermore, trainings were also given

in some areas of the personnel's expertise, such as Statistics and Medical Writing by, respectively, DATAMEDICA's Medical Statistician and Medical Writer.

The only training given by me was the one after an INFARMED's conference on Orphan Drugs. Being the backup CRA for all the rare diseases studies of DATAMEDICA put me in a privileged position when it came to deciding who was going to attend the conference. Accompanied by a more experienced CRA, everything that was said during the conference was written by me and by her. A PowerPoint presentation was then prepared by us in order to present what had been discussed at INFARMED. By presenting what we had heard at INFARMED to all the Clinical Research team, everyone was allowed to further understand orphan drugs and their approval in Europe. This is, in fact, a great way to give all DATAMEDICA members training in a specific area without having everyone spending time to attend the conferences.

These trainings were then evaluated by everyone who attended them. For doing that, a SOP Annex was created by me. That annex contained the evaluation sheet and the evaluation matrix. The first is a basic evaluation form, where the trainee has to evaluate the trainer according to several parameters. The presentation and the place it took place were also parameters to be evaluated. The evaluation matrix, on the other hand, was an excel file prepared to collect all the data from the aforementioned sheet. Once all data was transcribed, graphics and averages of each parameter were automatically generated. This allowed the trainer to quickly visualize how the trainees had evaluated his/her performance while remaining anonymized. The evaluation matrix could be filled by anyone but the trainer, who would only have access to the already completed matrix.

External trainings were also performed by DATAMEDICA's staff. During the internship, the host company was hired to give training on Statistics and Good Clinical Practices. For those trainings, certificates had to be created, as a template did not previously exist. Due to my ease in working with Microsoft Publisher 2016, certificates were asked to be created by me by the Quality Assurance Manager. The certificate was a rather easy template to create, as little information had to be displayed on it. To conclude the certificate, a separate spreadsheet was created for keeping track of the serial numbers already attributed.

2.6.5. Validation of Electronic Case Report Forms

eCRF validation was one of the activities performed in which a great eye for detail and constant hypothesis' creation was needed by me. After creating a CRF and implementing it on an online platform, its validation must be performed. Validating an eCRF requires testing all fields with every type of value, for obtaining, in the end of the study, a database with as few errors as possible. It is also an important task to understand if it is user-friendly, as some eCRFs may be longer than expected by the investigator.

This activity was done by me with two eCRFs, both in the scope of non-interventional studies in rare diseases. The first thing to do is to check if the eCRF matches the CRF draft, made on paper. After assuring the CRFs are a match, the validation of the fields must be made. Validating field is more than randomly writing words or numbers in a text box: it is about making sure only valid entries can be written in the eCRF. If, for example, the eCRF requires you to write the height of a person in centimetres, it should not accept values like 2 or even 300. This is the same for laboratory parameters, being the reason why validating the eCRF is a task to be performed by a person who can easily access the range values of exams or possible/feasible answers to a specific question. Verifying the branching of the eCRF is also something to be aware of. Branching is when different answers to a question lead to different questions or even pages. Not having this function working correctly can become a disaster for the entire data collection and to the people who are entering data in the eCRF, as the time required for doing such can double.

Despite not having many pages, performing those eCRFs validation during the internship was a time consuming activity. Detecting all the errors in the platforms, transmitting the information to the programmer, and verifying if the error was successfully corrected was a long lasting cycle. Considering me a person who tries to reach excellency and with a keen eye for detail, this was a perfect activity to execute during the internship, as both those characteristics were essential to complete this task.

3. DISCUSSION

This internship was a really enriching experience and fit like a glove in the conclusion of my academic life, at least for now. A huge amount of knowledge and hard and soft skills were acquired during these 8 months at DATAMEDICA. Some projects were more attractive, some required harder work than others but all of them contributed in their own way to my learning process, making me a better Clinical Research professional.

The decision to perform the internship at a CRO, in order to fulfil various activities, proved to be right, as a broad scope of clinical research related activities were completed. Performing it at DATAMEDICA was also a good decision, as it is believed by me that starting a professional career in a small company with a more "family" environment and where everyone performs various tasks is very educational. As a result, not only CRA related activities were accomplished but experience was also acquired by me in other tasks a CRO has to focus itself during the developing of a clinical research project.

In the beginning of the internship there was still a cloud on my mind whether the CRA job was suitable for me or even if it was going to be a challenging job rather than one which lacked interest. Entering DATAMEDICA believing the CRA position was stimulating was one of my main drivers before starting the internship. It was believed by me that this position would provide me with daily challenges, allowing me to learn something new every single day. Those expectations were thankfully met. Not only some projects made me eager to arrive at the host company and work on them every day, but also many challenges were faced throughout this journey, some overpassed easily than others. Being in such position allowed me to travel to some of the most important hospitals in the country and meet some of the people with most influence in specific pathologies in Portugal. Managing different investigators and other clinical research professionals' personalities was definitely a challenge during this internship and, without a doubt, one of the most fulfilling ones.

Working in centres without Study Coordinators was also a challenge. It made me realize how important they are, especially if Portugal wants to continue to increase its clinical trials numbers. Those numbers are diminished because centres and authorities take too long to evaluate processes. This is a turn down to investors and companies who want to bring trials to Portugal. However, with study coordinators, Hospital processes are done quicker and more effectively, leading to a decrease in the centre's approval time. By being present, they

also allow to change the paradigm of clinical trials doing no good to patients, as doctors can see their constant work. Study coordinators are also a great help in monitoring activities, as they are easily reachable when CRAs try to solve any issues with centres and/or principal investigators. Moreover, an experienced Study Coordinator will fill the CRFs with fewer errors than investigators would, thanks to their constant contact with such forms. This decreases the time spent by CRAs at the study centres, allowing them to have time and focus on other important activities. In sum, if a good relationship is created between CRAs and Study Coordinators, the centres and companies will be more pleased with the present results, resulting in a win-win situation.

Regarding the many activities performed during the internship, being able to work on different areas and activities allowed me to have a glimpse on almost all fields of activity of a Full Service CRO. The activities most enjoyed by me were definitely the CRA ones. Despite some of the CRA activities not requiring scientific expertise, and consequently not being stimulating, the ones which require such knowledge make it worth it. For example, although not intellectually demanding, data entry helped me to be (even) more methodical. It was like this because data-entry deadlines had to be fulfilled and to do so, it had to be done as accurately and fast as possible. By transforming a non-demanding task into one who required full focus and discipline, data-entry became bearable and not as boring as it was initially expected by me.

In fact, it is truly believed by me that the CRA job can be performed by almost any person who has some health sciences academic background. Even though, the more preparation that person has relating to regulatory and monitoring activities, the most he/she is going to be prepared to successfully accomplish the CRA tasks.

Having had a B.Sc. which learning method was “Problem Based Learning” helped me being a more independent and adaptable professional. Through this method, students are encouraged to learn by themselves, guided by a question or problem. This is extremely important because of not being stranded to just one therapeutic area but too many of them, as learning, comprehending and adapting to different pathologies become easier. During the internship this was a clear fact, as studies in many therapeutic areas were addressed by me without much difficulty.

The objectives outlined by me for the internship in its beginning were met. Being introduced to the professional world was one of my main goals, certainly achieved as expressed

throughout this report. One of the following objectives was to apply and consolidate the knowledge acquired during my B.Sc. and M.Sc., by either applying the main methods used in the conception and development of clinical studies and by the submission to several entities of those clinical studies. Many submissions were performed by me during the internship at the host company, especially submissions to Hospital's ABs and correspondent Ethic Committees. Several submissions were also made to CNPD, whereas few were made to both CEIC and INFARMED.

By accompanying SIVs, monitoring visits and COVs and writing some of the correspondent reports, another objective was successfully completed, as techniques were learned and skills inherent to the clinical studies' monitoring were developed. During these visits, the assurance the clinical study team was following the protocol and keeping the patients safe was performed by me. As specified in the internship agreement, this particular task is essential in order to ensure the high quality of the data obtained. All this work, as well as every activity performed during the internship at the host company was performed according to the ICH-GCP and DATAMEDICA's SOPS. Following the ICH-GCP is a good principle, as all CROs in the country follow these guidelines. Furthermore, by performing the activities according to the host company's SOPs my capacity to follow a standardized procedure was tested. Not only it made me realise that in almost every situation there is a procedure to be followed, it also allowed me to become aware of such practices, transversal to every company in the pharmaceutical field. Taking this into account, my capacity to somewhere in the future entering in another CRO or even pharmaceutical company was somehow improved by accomplishing this internship objective.

Additionally, competences regarding team work and establishment of interpersonal relations were further developed, not only with DATAMEDICA's co-workers but also through all the meetings had outside the office with the study teams and/or sponsors. Helping the host company in other projects not directly related with clinical studies monitoring was a reality throughout the internship. This was gladly done, as being involved in several activities allowed me to develop skills inherent to other work fields. It also enabled me to understand the situations from other perspective. This was a capital gain to my present and future professional experience, as it now allows me to think as a data manager or eCRF designer instead of a CRA in specific situations. Throughout my trainee experience a constant and continuous learning process was maintained, which was also one of my objective for this

internship. Even today, as a Clinical Research professional, this learning process is kept "alive", allowing me to acquire knowledge every day at work.

From every DATAMEDICA's project integrated by me something new was learned. Some learning experiences were good, some were not as good, but in the end all those experiences somehow helped me to become a better professional and not to make the same "mistake" twice. Upon my entry at DATAMEDICA, every person helped me to quickly fit in the company. They spent some of their time explaining me what to do in specific situations, allowing me to have a great perspective on how some tasks were performed. All the lack of guidance felt on the beginning of the internship was rapidly addressed by my colleagues, who were at all time giving me both support and tasks to perform. Being involved in several activities from different projects allowed me to become prepared for future experiences and work related tasks which became capital later on during the internship.

4. CONCLUSION

The internship performed as a CRA in DATAMEDICA was, without a doubt, very useful to connect the knowledge acquired during the B.Sc. in Biomedical Sciences and M.Sc. in Pharmaceutical Medicine with the work marketplace. All the knowledge and skills were put together in a new on-the-job perspective. This allowed me to strengthen and solidify all the concepts learned during both the degrees and to acquire new skills and work methods which would not be possible without the internship.

That being said, DATAMEDICA's internship was an important experience, especially considering all the activities performed throughout the 8 months present there. All the objectives were achieved by me. Having a role in some of the most critical projects of the host company allowed me to improve my skills in clinical studies' related activities, such as clinical studies monitoring, project management and study documents' development. Almost every working day proved to be a challenge and an opportunity to learn something new, which was my main driver to get up and go to work during this experience.

Not being only focused on monitoring but truly in all the tasks which are supposedly performed by a CRA was rewarding, increasing my hard and soft skills in clinical research. The pinnacle of this internship was to become the CRA responsible for 7 projects in the month of February. This action was interpreted by me as proof the host company believed in my work and saw in me a trustworthy and capable CRA. My willingness to learn and work put in every project were the key aspects highlighted by the Chief Executive Officer when offering me a contract to stay in DATAMEDICA at the end of the internship.

Despite feeling accomplished after this internship and 5 years of university, much is yet to be learned as a Clinical Research professional, making me crave for greater challenges, namely stimulating projects within challenging therapeutic areas. To sum up, this was the step which helped me defining the next short, mid and long-term goals of my professional journey.

5. REFERENCES

1. ICH. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance [Internet]. ICH; 1996. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
2. DATAMEDICA - Consultoria e Serviços em Bioestatística Lda. DATAMEDICA [Internet]. [cited 2015 Sep 20]. Available from: www.datamedica.pt
3. National Institutes of Health (NIH). Glossary & Acronym List [Internet]. 2013 [cited 2015 Nov 19]. Available from: http://grants.nih.gov/grants/glossary.htm
4. APIFARMA, PricewaterhouseCoopers. Ensaios Clínicos em Portugal [Internet]. 2013. Available from: https://www.apifarma.pt/publicacoes/siteestudos/Documents/EstudoInvestig.Clinica em Portugal. jun.2013.vf.pdf
5. National Institutes of Health (NIH). Learn About Clinical Studies [Internet]. 2014 [cited 2015 Nov 23]. Available from: https://clinicaltrials.gov/ct2/info/understand
6. Assembleia da República. Lei n.º 21/2014, de 16 de abril. Diário da República; 2014.
7. National Health System (NHS). Clinical trials and medical research - Phases of trials [Internet]. 2015 [cited 2015 Nov 25]. Available from: http://www.nhs.uk/conditions/Clinical-trials/Pages/Phasesoftrials.aspx
8. U.S. Food and Drug Administration (FDA). Step 3: Clinical Research [Internet]. 2015 [cited 2015 Nov 25]. Available from: http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm
9. Griffin JP. The Textbook of Pharmaceutical Medicine. 6th ed. Griffin JP, editor. Wiley-Blackwell; 2009.
10. Wellcome Genome Campus. What is a clinical trial? [Internet]. 2014 [cited 2015 Dec 22]. Available from: http://www.yourgenome.org/facts/what-is-a-clinical-trial
11. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov [Internet]. 2010;9(3):203–14. Available from: http://www.nature.com/doifinder/10.1038/nrd3078
12. Hirschler B, Berkrot B. Pfizer walks away from $118 billion AstraZeneca takeover fight [Internet]. 2014 [cited 2015 Dec 24]. Available from: http://www.reuters.com/article/us-astrazeneca-pfizer-idUSBREA3R0H520140526
13. Pierson R, Berkrot B. Pfizer to buy Allergan in $160 billion deal [Internet]. 2014 [cited 2015 Dec 24]. Available from: http://www.reuters.com/article/us-allergan-m-a-pfizer-idUSKBN0TB0UT20151124
14. Noronha N. Viagra já tem 58 genéricos desde perda de patente em janeiro [Internet]. 2014 [cited 2015 Dec 24]. Available from: http://lifestyle.sapo.pt/saude/noticias-saude/artigos/viagra-ja-tem-58-genericos-desde-perda-de-patente-em-janeiro
15. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010 Mar;9(3):203–14.

16. European Medicines Agency. Clinical trials in human medicines [Internet]. 2015 [cited 2015 Dec 1]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

17. European Commission. Proposal for a Clinical Trials Regulation - Questions and answers [Internet]. 2012 [cited 2015 Dec 1]. Available from: http://europa.eu/rapid/press-release_MEMO-12-566_en.htm

18. European Medicines Agency. EudraCT Public Web Report for December 2015 [Internet]. 2016 [cited 2016 Feb 9]. Available from: https://eudract.ema.europa.eu/docs/statistics/EudraCT_Statistics_2015/EudraCT Public Report_Stats_Dec_2015.pdf

19. European Medicines Agency. Who we are [Internet]. 2015 [cited 2015 Dec 9]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000092.jsp&mid=WC0b01ac0580028a43

20. European Medicines Agency. What we do [Internet]. 2015 [cited 2015 Dec 9]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42

21. European Parliament. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 [Internet]. Official Journal of the European Union; 2004. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=EN

22. European Commission. 50 years of EU pharma legislation - Reflecting on the past - striving for the future [Internet]. 2015 [cited 2015 Dec 8]. Available from: https://ec.europa.eu/commission/2014-2019/andriukaitis/announcements/50-years-eu-pharma-legislation-reflecting-past-striving-future_en

23. Fintel B, Samaras AT, Carias E. The thalidomide tragedy: lessons for drug safety and regulation [Internet]. 2009 [cited 2015 Dec 8]. Available from: https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation

24. Young LY, Kradjan WA, Guglielmo BJ, Alldredge BK, Corelli RL, Williams BR, et al. Applied Therapeutics: The Clinical Use of Drugs. 9th ed. Lippincott Williams & Wilkins; 2008.

25. ICH. History [Internet]. [cited 2015 Dec 8]. Available from: http://www.ich.org/about/history.html

26. ICH. Vision [Internet]. [cited 2015 Dec 8]. Available from: http://www.ich.org/about/vision.html

27. ICH. Quality Guidelines [Internet]. [cited 2015 Dec 8]. Available from: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

28. ICH. Safety Guidelines [Internet]. [cited 2015 Dec 8]. Available from: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html

29. ICH. Efficacy Guidelines [Internet]. [cited 2015 Dec 8]. Available from: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

30. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomed Imaging Interv J [Internet]. 2008 Jan;4(1). Available from: http://www.biij.org/2008/1/e5/e5.pdf

31. ICH. Multidisciplinary Guidelines [Internet]. [cited 2015 Dec 8]. Available from: http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html

32. INFARMED. Medicines and health products regulatory authority [Internet]. [cited 2015 Dec 11]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/ABOUT_INFARMED

33. Comissão de Ética para a Investigação Clínica (CEIC). CEIC - Missão [Internet]. [cited 2015 Dec 12]. Available from: www.ceic.pt /portal/page/portal/CEIC/QUEM_SOMOS/MISSAO

34. CNPD. O que é a CNPD [Internet]. [cited 2015 Dec 12]. Available from: www.cnpd.pt /bin/cnpd/acnpd.htm

35. INFARMED. Evolução Anual 2005-2015 [Internet]. 2016 [cited 2015 Jan 20]. Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/ENSAIOS_CLINICOS/ESTATISTICAS/Evolu%E7%E30 Anual 2005 - 2015

36. European Medicines Agency. Ongoing Clinical Trials in EU Member Countries [Internet]. 2016 [cited 2016 Jan 1]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=&country=at&country=be&country=bg&country=hr&country=cy&country=cz&country=dk&country=ee&country=fi&country=fr&country=de&country=gr&country=hu&country=ie&country=it&country=lv&country=lt&count

37. European Union. EU member countries [Internet]. 2014 [cited 2015 Dec 22]. Available from: http://europa.eu/about-eu/countries/member-countries/

38. European Commission. Detailed guidance on the European clinical trials database (EUDRACT Database) [Internet]. European Commission; 2003. Available from: http://ec.europa.eu/health/files/eudralex/vol-10/13_cp_and_guidance_eudract_april_04_en.pdf

39. MacDonald G. CRAs spend less than half their time in on-site monitoring taks, says Tufts [Internet]. 2012 [cited 2015 Feb 15]. Available from: http://www.outsourcing-pharma.com/Clinical-Development/CRAs-spend-less-than-half-their-time-in-on-site-monitoring-tasks-says-Tufts

40. TransCelerate BioPharma Inc. Risk-Based Monitoring Update – Volume I [Internet]. 2014 [cited 2016 Feb 20]. Available from: http://www.transceleratebiopharmainc.com/wp-content/uploads/2014/01/TransCelerate-RBM-Update-Volume-I-FINAL-27JAN2014.pdf